

Treatment of Iron-deficiency Anemia in Patients with Subclinical Hypothyroidism

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ABSTRACT

OBJECTIVE: Subclinical hypothyroidism is a health state that is associated with hypercholesterolemia, infertility, iron-deficiency anemia, and poor obstetric outcome. This article summarizes the results of a prospective clinical investigation of whether treatment of subclinical hypothyroidism and iron-deficiency anemia with a combination of levothyroxine *plus* iron salt would be superior to each treatment alone.

METHODS: In a randomized, double-blind, active-controlled trial, 60 patients with subclinical hypothyroidism and iron-deficiency anemia received iron salt + placebo (20 patients), levothyroxine + placebo (20 patients), or levothyroxine + iron salt (20 patients) for 3 months. Change from baseline (before) to end of study (after) in hemoglobin, ferritin, and thyroid-stimulating hormone levels were compared among groups.

RESULTS: The increase from baseline in hemoglobin and ferritin in the levothyroxine + iron group was superior to the other groups, in which a decrease in thyroid-stimulating hormone in the 2 groups that received levothyroxine was superior to the group treated with iron salt.

CONCLUSION: Subclinical hypothyroidism was investigated in iron-deficient patients with no acceptable response to iron salt alone. A combination of levothyroxine and iron salt is better than each one alone.

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Subclinical hypothyroidism is a condition with elevated serum thyroid-stimulating hormone in the setting of normal total or free thyroxine (T4) concentration in serum.¹ Some patients may have vague and nonspecific symptoms of subclinical hypothyroidism, but most affected individuals are asymptomatic and identified during routine blood tests. The prevalence of subclinical hypothyroidism has been reported to be approximately 4% to 10% in different geographic populations.¹ Screening and management of subclinical hypothyroidism are known to be challenging and therefore of interest to be better understood. Subclinical hypothyroidism has been long associated with hypercholesterolemia, atherosclerosis, cardiovascular mortality, infertility, poor obstetric

outcome, neuropsychiatric symptoms, unprovoked deep vein thrombosis, and common bile duct stones.¹⁻⁵

Conditions that increase iron loss, increase demand for iron, or decrease iron intake or absorption can produce iron-deficiency anemia. In patients with iron-deficiency anemia, clarifying the specific clinical conditions that cause iron deficiency is important.

Thyroid hormones have some effects on hematopoiesis. Among patients with hypothyroidism, normocytic normochromic anemia is relatively common, which is due to a decrease in red blood cell mass and hypoproliferation of erythroid progenitors.⁶ Thyroid hormones may affect hematopoiesis through an increase in erythropoietin production or hematopoietic factors by nonerythroid cells.⁷ Anemia in hypothyroid patients in the setting of normal serum iron, vitamin B₁₂, and folate could be normalized with levothyroxine administration.⁸ However, hypothyroidism also has been associated with low levels of iron, folate, and vitamin B₁₂.⁷ Iron-deficiency anemia particularly has been reported in patients with hypothyroidism or subclinical hypothyroidism.^{1,2}

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Treatment of subclinical hypothyroidism with levothyroxine in patients with iron-deficiency anemia has beneficial effects on iron status and blood count indices.¹ However, to the best of our knowledge, no published study has compared levothyroxine therapy alone with levothyroxine and iron salt combined for treating patients with both iron-deficiency anemia and subclinical hypothyroidism present. The present study compares the results of different treatment modalities in these patients. We hypothesized that prescription of levothyroxine and iron salt together is superior to each one when administered as a single therapy.

MATERIALS AND METHODS

Study Design

Newly diagnosed individuals with subclinical hypothyroidism were studied at the endocrinology and metabolism outpatient clinic at Bushehr University of Medical Sciences, Bushehr, Iran. From January to November 2010, a total of 305 patients with subclinical hypothyroidism (thyroid-stimulating hormone = 4.5–10 mU/L and normal fT4 and fT3) checked into the clinic. Of the 305 patients, 60 had newly diagnosed iron-deficiency anemia (hemoglobin < 12 g/dL and ferritin < 25 µg/L for women; hemoglobin < 13.5 g/dL and ferritin < 30 µg/L for men).

None of the patients had any indication (eg, signs and symptoms of hypothyroidism, fatigue, constipation, depression, hyperlipidemia with total cholesterol > 200 mg/dL or triglyceride > 250 mg/dL, positive antithyroid peroxidase antibody > 120, enlarged thyroid, pregnancy, ovulatory dysfunction, infertility, and thyroid-stimulating hormone > 10 mU/L) requiring levothyroxine therapy.

All female patients were asked about their menstrual period duration, frequency, and amount of bleeding. Patients with a menstrual period lasting more than 5 days or more than usual amount of bleeding were excluded from study. Patients with genitourinary blood loss; gastrointestinal blood loss; hemolytic anemia; prior thyroid, cardiovascular, respiratory, renal, and liver diseases; any chronic diseases, including diabetes mellitus, uncontrolled hypertension, adrenal insufficiency, and other endocrine disorders; or any cause for anemia other than iron deficiency and subclinical hypothyroidism were excluded from the study.

The patients were informed of the study protocol, including the risks and benefits of the treatment modalities, and informed consent forms were signed before participation in the study. The study was approved by the ethics committee of the Research Affair of Bushehr University of Medical Sciences. All patients were evaluated by an endocrinologist and a hematologist before and after therapy. Medical history

and physical examination blood sampling for complete blood count, white blood cell differential, reticulocyte count, fasting blood glucose, cholesterol, triglyceride, blood urea nitrogen, creatinine, sodium, potassium, serum iron, total iron-binding capacity, ferritin, albumin, globulin, as-

partate aminotransferase, alanine aminotransferase, lactate dehydrogenase, total bilirubin, and direct bilirubin were performed. Stool samples for occult blood and urine analysis for hematuria were completed. Peripheral blood smears of all patients were seen by the collaborating hematologist to rule out other causes of anemia. Stool examinations for occult blood with guaiac test, leukocytes, and parasites with microscopic examination were performed 3 times for all patients. Urine dipstick examination and microscopic examination of urine after centrifugation were performed to rule out pro-

teinuria, glucosuria, pyuria, and hematuria. Complete blood counts were performed with the Sysmex XS-800i Fluorescence Flowcytometry. Serum chemistries were studied using the Slectra XL. The Berthold chemiluminescence method was used to assay thyroid function tests, ferritin levels, and antithyroid peroxidase antibody.

Patients with both iron-deficiency anemia and subclinical hypothyroidism (N = 60) were referred to the investigator for random assignment to ferrous sulfate (65 mg/d) + matching placebo, levothyroxine (50 µg/d) + matching placebo, or ferrous sulfate (65 mg elemental iron/d) + levothyroxine (50 µg/d), and they were numbered as treatment groups 1, 2, and 3, respectively. Each bottle contained medication for 90 days of therapy. Bottles were each placed in separate but uniform boxes, and every patient received 2 boxes according to their randomization. Compliance was assessed by counting tablets and asking the patients specific questions at the end of the study. The patients were asked to contact the clinic if they experienced any adverse events during therapy, and an assessment of any complications was performed at the end of the study.

All patients were evaluated twice (before and after therapy) during the study period. Patients were instructed to have a normal diet and advised to avoid consumption of mineral or vitamin supplements and an excess amount of tea and bran foods. The study primary objective was to determine changes from baseline (before) in hemoglobin to the end of the study. Secondary end points included serum ferritin and thyroid-stimulating hormone change from baseline to the end of study. All patients were able to contact the clinic by telephone during the study period as needed. Of note, 100% of the patients (N = 60) completed the study per protocol.

CLINICAL SIGNIFICANCE

- Recent studies revealed an association between iron-deficiency anemia and subclinical hypothyroidism, and treatment with levothyroxine can improve the response to iron salt.
- This study revealed that a combination of levothyroxine and iron salt in patients with iron-deficiency anemia and subclinical hypothyroidism is superior to each one alone.

Table 1 Baseline Characteristics and After Treatment Parameters

Parameters	Treatment Groups*		
	Iron + Placebo	Levothyroxine + Placebo	Iron + Levothyroxine
N	20	20	20
Gender (n %)			
Male	10 (50%)	10 (50%)	10 (50%)
Female	10 (50%)	10 (50%)	10 (50%)
Age (y)	32.8 ± 6.83	33.6 ± 6.80	33.8 ± 6.79
Weight (kg)	74.4 ± 9.42	74.0 ± 10.93	73.5 ± 10.5

*Age and weight are reported as mean ± standard deviation. There were no statistical differences between groups.

Statistical Analyses

No formal power analysis was conducted to estimate the sample size in the study. After randomizing 61 patients into the study at a 1:1:1 ratio stratified by gender, enrollment stopped because of the unavailability of additional patients meeting inclusion and exclusion criteria. One patient was later lost to follow-up, and 60 patients equally randomized between groups and gender within each group were used to evaluate the objectives of the study. Normally distributed data are reported as mean ± standard deviation, and count data are reported by N (%). Paired *t* test was used to compare before and after measurements in each treatment group for each of the primary and secondary end points. Analysis of variance model was used to compare changes from baseline in hemoglobin, serum ferritin, and thyroid-stimulating hormone across treatment groups and baseline characteristics (age, gender, and weight). A *P* value < .05 was considered statistically significant. Data processing and statistical analysis were performed by using SPSS 15.1 (SPSS Inc, Chicago, Ill).

RESULTS

No treatment-related adverse events were reported in any of the treatment groups. All patients were asymptomatic and had

no goiter and positive thyroid peroxidase antibody. The observed range of menstrual period for female patients included in the study was 2 to 5 days and not different between groups.

Baseline characteristics and laboratory data for all treatment groups are shown in **Tables 1** and **2**. There were no statistical differences found at baseline between the groups with regard to gender, age, weight (**Table 1**), hemoglobin, thyroid-stimulating hormone, and ferritin (**Table 2**). There were no statistically significant differences in the menstrual blood loss between the treatment groups before and during the study. All stool examination results for occult blood were negative. Within each treatment group, before and after measurements were compared. There were no significant differences in hemoglobin, ferritin, and thyroid-stimulating hormone in the iron + placebo treatment group. There were no significant differences in hemoglobin or ferritin in the levothyroxine + placebo treatment group, but thyroid-stimulating hormone decreased significantly (*P* < .001). There were significant increases in hemoglobin and ferritin and significant decreases in thyroid-stimulating hormone in the iron + levothyroxine treatment group (*P* < .001) (**Table 2**). Hemoglobin and ferritin normalized (hemoglobin ≥ 12 g/dL and ferritin ≥ 10 ng/mL for women; hemoglobin ≥ 13.5 g/dL and ferritin ≥ 29 ng/mL for men) for most subjects treated with iron + levothyroxine therapy but not with the other 2 treatments. Thyroid-stimulating hormone normalized (thyroid-stimulating hormone ≤ 4.5 μIU/mL) for all patients in the levothyroxine + placebo and iron + levothyroxine treatment groups but not in the iron + placebo treatment group.

An increase in hemoglobin was most pronounced in the iron + levothyroxine treatment group (1.17 g/dL) compared with the levothyroxine + placebo group (0.26 g/dL) and iron + placebo group (0.005 g/dL) (**Table 3**). This increase in hemoglobin was highly significant (*P* < .0001) when the iron + levothyroxine treatment group was compared with either of the other treatment groups. A similar statistical benefit in ferritin increase was observed across treatment groups (*P* < .0001), with a clear advantage for the iron + levothyroxine group with an average 10.78 ng/mL increase in the values compa-

Table 2 Baseline Characteristics and After Treatment Parameters

Parameters	Treatment Groups*									Baseline Comparison
	Iron + Placebo			Levothyroxine + Placebo			Iron + Levothyroxine			
	Before	After	<i>P</i> Value†	Before	After	<i>P</i> Value†	Before	After	<i>P</i> Value†	
Hb (g/dL)	11.67 ± 0.983	11.67 ± 1.07	.956	12 ± 0.946	12.26 ± 0.957	.101	11.7 ± 0.988	12.88 ± 0.831	<.001	.504
Ferritin (ng/mL)	16.75 ± 6.06	17.55 ± 5.26	.572	17.25 ± 5.68	17.77 ± 6.37	.501	17.1 ± 5.54	27.72 ± 5.58	<.001	.961
TSH (μIU/mL)	8.12 ± 1.22	7.54 ± 1.81	.136	8.36 ± 0.917	2.61 ± 1.32	<.001	8.04 ± 1.43	2.9 ± 1.71	<.001	.683

Hb = hemoglobin; TSH = thyroid-stimulating hormone.

*Summaries are reported as mean ± standard deviation.

†*P* values from paired *t* test.

‡*P* values compare "before" values between groups.

Table 3 Comparison of Before and After Treatment Differences Between Groups

Change From Baseline (After, Before)	Treatment Groups*			P Value		
	Group 1: Iron + Placebo	Group 2: Levothyroxine + Placebo	Group 3: Iron + Levothyroxine	Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
ΔHb, g/dL	0.005 ± 0.39	0.26 ± 0.675	1.17 ± 0.59	NS	<.0001	<.0001
ΔFerritin, ng/mL	0.722 ± 5.32	0.61 ± 3.77	10.78 ± 5.19	NS	<.0001	<.0001
ΔTSH, mIU/L	0.580 ± 1.67	5.75 ± 1.41	5.12 ± 2.25	<.0001	<.0001	NS

Hb = hemoglobin; NS = not significant; TSH = thyroid-stimulating hormone.

*Summaries are reported as mean ± standard deviation.

red with 0.611 and 0.722 ng/mL increases in the levothyroxine + placebo and iron + placebo groups, respectively.

An increase in hemoglobin and ferritin in each group had no significant differences between men and women. An increase in hemoglobin and ferritin in female patients was less than in male patients but without statistical significance. Female patients did not report a change in menstrual period (duration, amount, and frequency of bleeding) during the study period. No significant differences between men and women in each group were detected in thyroid-stimulating hormone.

Both the iron + levothyroxine and levothyroxine + placebo groups demonstrated superiority ($P < .0001$) over the iron + placebo group with regard to a decrease in thyroid-stimulating hormone, 5.12 and 5.75 mIU/L, respectively, over 0.58 mIU/L in the iron + placebo group.

DISCUSSION

It is common and acceptable to treat patients of all ages with subclinical hypothyroidism with levothyroxine when thyroid-stimulating hormone is > 10 mU/L^{9,10} and nonelderly patients when thyroid-stimulating hormone is > 4.5 mU/L when one of the following is present: symptoms suggestive of hypothyroidism, presence of high titers of antithyroid peroxidase antibodies, thyroid enlargement,¹¹ or pregnancy. Patients with iron-deficiency anemia should be treated with iron-replacement therapy and evaluated to determine the cause of iron deficiency. Furthermore, subclinical hypothyroidism has a known association with iron-deficiency anemia,^{1,2} and all patients with iron-deficiency anemia who have no definite cause of blood loss or iron malabsorption may need to be examined for subclinical hypothyroidism. Both diseases may need to be treated if no acceptable response to iron salts is achieved. The causes of iron-deficiency anemia basically are low iron intake, iron malabsorption, and blood loss. Subclinical hypothyroidism may cause iron malabsorption or a decrease in iron incorporation, and as a result an increase in iron loss.

The study results demonstrated that treatment of patients with subclinical hypothyroidism and iron-deficiency anemia with a combination of iron + levothyroxine resulted in a favorable outcome compared with treatment of patients with monotherapy of iron or levothyroxine alone. Hemoglobin as

the leading indicator for improvement in anemia and thyroid-stimulating hormone as an indicator for subclinical hypothyroidism both improved significantly ($P < .0001$) in patients treated with the combination therapy compared with monotherapy (Table 3). Our study showed that iron or levothyroxine replacement alone in the patients with iron-deficiency anemia and subclinical hypothyroidism did not improve hemoglobin and ferritin levels, and that the best results were achieved with the combined prescription of iron + levothyroxine. No increase in ferritin level was observed in patients treated with iron or levothyroxine alone, indicating that correcting thyroid function is necessary to improve iron status in patients with subclinical hypothyroidism and iron-deficiency anemia, most likely because of improved absorption of iron or prevention of iron loss. These findings mean that the patients with iron-deficiency anemia who have no acceptable response to iron replacement should be studied for possible causes, including subclinical hypothyroidism, and if the 2 conditions coexist, levothyroxine therapy should be added to iron salt. Furthermore, iron salt alone had no significant effects on thyroid-stimulating hormone level when compared with the other 2 groups treated with levothyroxine or iron + levothyroxine. Prescription of iron salt in the patients with iron-deficiency anemia and subclinical hypothyroidism had no significant effect on thyroid-stimulating hormone level, which differs from the results obtained by Gokdeniz et al,¹² who showed that iron replacement in patients with iron-deficiency anemia and normal thyroid function significantly decreases thyroid-stimulating hormone level and increases free T4 level. Moreover, some studies showed that iron deficiency with or without anemia has adverse effects on thyroid physiology.^{13,14} Iron-deficiency anemia can affect thyroid metabolism through several mechanisms, such as decreased oxygen transport of anemia (similar to hypoxia), influence of iron deficiency on iodine deficiency disorders through alteration of central nervous system control of thyroid metabolism, and modification of nuclear T3 binding and altered thyroid peroxidase activity.¹⁵ Iron supplementation also has some beneficial effects on goiter in iodine-deficient patients with iron deficiency.^{16,17} We did not observe a significant effect of iron-replacement therapy on thyroid-stimulating hormone level, which may be

due to concomitant iodine deficiency or an insufficient power of the iron effect on thyroid-stimulating hormone in the setting of hypothyroidism or levothyroxine prescription. As a result, considering iron replacement therapy to correct abnormal thyroid function, especially in the absence of iron-deficiency anemia, does not seem to be reasonable, and further studies are needed to clarify this finding better.

Hypothyroidism is associated with iron-deficiency anemia, pernicious anemia, celiac disease, small intestine bacterial overgrowth, gastric atrophy, and decreased gut motility.^{1,18,19} Hypothyroid patients with iron-deficiency anemia respond adequately to levothyroxine and iron salt. Furthermore, hypothyroidism may have some effects on iron absorption by a decrease in acid secretion. Gastric acid degrades the organic iron complex (vegetable protein), reduces the trivalent mineral to ferrous iron, and improves proximal small-bowel absorption of iron. As a result, levothyroxine prescription can reverse the deleterious effects of thyroid hormone deficiency on iron absorption.^{1,18,19}

Hypothyroid women in their childbearing years may develop iron deficiency secondary to menorrhagia, and levothyroxine can improve the hemoglobin level by affecting menstrual blood loss. In our study, female patients did not report a change in their menstrual period or the amount of bleeding during the study period. Furthermore, male and female patients showed an approximately equal amount of hemoglobin and ferritin increment in each group. As a result, levothyroxine use in patients with subclinical hypothyroidism had no significant effect on menstrual bleeding in our study, but we should keep in mind that there were too many subjects in each group to stratify sex; thus, the statistical analysis had insufficient power to reveal any gender effect.

CONCLUSIONS

To the best of our knowledge, our study is the first study to compare iron salt, levothyroxine, and iron salt + levothyroxine in the treatment of subclinical hypothyroidism and iron-deficiency anemia. Our results indicated that levothyroxine + iron salt was superior to other treatment modalities. It is important to consider subclinical hypothyroidism when iron salt is not effective in iron-deficiency anemia, especially in endemic areas of iodine deficiency and goiter. Therefore, we suggest prescription of levothyroxine + iron salt in patients with coexistent subclinical hypothyroidism and iron-deficiency anemia.

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